D 56

United States
Environmental Protection
Agency

Health Effects Research
Laboratory
Research Triangle Park NC 27711

Research and Development

EPA-600/S1-81-054 Sept. 1981

EPA

Project Summary

Respiratory Carcinogenicity of Diesel Fuel Emissions

NEWARK PUBLIC LIBRARY

NOV 24 1981

U. S. GOVT. PUBS.
DEPOSITORY 376

Alan M. Shefner

This program evaluated the possible respiratory carcinogenic effects of diesel fuel emission particles and organic extracts of these particles in suitable animal models. The Schreiber method for localized tumor induction was the model chosen to initiate this study because of previous experience in its use and its observed rapid response time with certain known direct acting carcinogens. Subsequently, studies were to be initiated using the Saffiotti technique for intratracheal instillation for evaluation of life-time effects.

The program was initially planned for a three-year period with the major emphasis during the first year to be placed on short-term studies with the Schreiber model. Shortly after program initiation a scientific review meeting was held on the Diesel Emission Health Effects Research Program. As a result of this meeting and other program considerations concerning risk assessment utility, emphasis under this grant was gradually shifted to the utilization of the Saffiotti intratracheal instillation model. In addition, program plans were modified to include the assessment of coke oven extract, roofing tar extract, and cigarette smoke condensate on which a human epidemiologic data base existed.

As a result of those considerations, this grant was terminated after one year and an extensive study utilizing the Saffiotti technique was initiated under EPA Grant No. R806929-01-0 on September 1, 1979.

This Project Summary was developed by EPA's Health Effects Research Laboratory, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction and Summary

This grant was initiated to provide information relating to the potential respiratory carcinogenicity of diesel emission products. Emphasis was placed on the Schreiber model for localized tumor induction since it offered the possibility of a more rapid determination of adverse effects. Three initial experiments were carried out using the Schreiber technique in order to determine dose ranges of diesel extract suitable for future experiments. A number of solvent mixtures including dimethyl sulfoxide, propylene glycol, ethanol and saline were investigated for their ability to solubilize the extract at desired concentrations.

Although it proved possible to prepare and test extracts by this technique, it was decided not to continue with studies using this method of treatment. The localized treatment method cannot be used with particle suspensions so no direct comparison of the carcinogenic potential of diesel fuel emission particles (DP) and diesel fuel emission extract (DFE) can be carried out. In addition, this technique has not been widely used and it has not been demonstrated that the trachea is responsive to the

EP 1.89/2:

READEX FICHE

classes of combustion products that are present in DFE. Furthermore, the total dose of test material delivered to the hamster cannot be readily determined in this procedure. The concentration of test material to which the test animals are exposed is known, but how much of the test material is retained by the animal following the reabsorption phase of the intubation cycle is uncertain.

Thus, it was concluded that while the method is of potential interest as a research tool, program emphasis was to be placed on carcinogenicity trials using the better established intratracheal instillation method of Saffiotti.

An experiment was then carried out to provide information for selection of doses for the chronic study of diesel particles by the Saffiotti method. Diesel particles and DP-Fe_2O_3 mixtures were prepared by ball milling. Hamsters were treated at weekly doses of 1, 3, 5, and 10 mg. Animals at the 10 mg weekly level were treated twice weekly with doses of 5 mg each. Hamsters were held for 5 weeks following the 15 weeks of treatment, survivors were sacrificed, and tissues were processed for histopathologic examination. Twice weekly treatments with 5 mg DP or with 5 mg DP admixed with 5 mg of Fe_2O_3 led to a decreased weight gain as compared to control animals also receiving twice weekly instillations.

Microscopic examination of histologic sections of hamsters in this study showed that a variety of lung lesions occurred in treated animals that were either absent in control hamsters or present to a lesser extent. The degree of severity and frequency of occurrence of hyperplastic and metaplastic changes in lung tissue of hamsters given twice weekly treatments of 5 mg DP each plus the decreased weight gain observed in these treatment groups led to the conclusion that the high dose selected for the chronic study would be 5 mg of diesel particles, once weekly, for 15 weeks.

A limited study of lung clearance of diesel particles was carried out on a small group of hamsters. Each animal was administered a single dose of 5 mg DP by intratracheal instillation and pairs of animals were killed at 1 hour, 8 days, 30 days and 60 days post treatment. The lungs and trachea of one animal at each time period were photographed and lung and trachea from the second animal were processed for histopathologic examination.

Photographic reproductions of the lungs and trachea of animals in this study showed that the particles were dispersed throughout the lung tissue as well as the trachea at one hour post instillation. Eight days after the instillation the particles were still very prevalent in the lungs, but appeared to be mostly cleared from the trachea. At 30 days post instillation, the particles remained heavily concentrated in the lungs. Gross observation of a hamster sacrificed 60 days post instillation showed particles still remaining in the lung but in apparently reduced amounts.

The study demonstrated that the Saffiotti method of intratracheal instillation led to good dispersion of the diesel particles throughout alveoli, bronchioles, and bronchi. Although no quantitative estimates of clearance rates can be obtained, the photographic representations and tissue sections both showed that diesel particles were still present in good number even 60 days after a single instillation of 5 mg of DP.

Conclusions and Recommendations

Following a presentation at a Diesel Emission Health Effects Program meeting in December of 1978 and subsequent program discussions it was decided to deemphasize work using the Schreiber model and to initiate dose range toxicity studies by the Saffiotti intratracheal instillation technique.

This decision was reached for three primary reasons.

1. The Saffiotti method offers a proven and widely accepted model for inhalation effects.
2. Total dose administered is known with the Saffiotti technique but not for the Schreiber method.
3. The Saffiotti method is ideal for the evaluation of diesel emission particles which cannot be tested using the Scheiber technique.

Since EPA's program for the evaluation of the health effects of diesel fuel emissions was aimed at developing a series of potency comparisons between diesel emissions and other materials on which there existed an epidemiologic data base, it was recommended that this respiratory carcinogenesis study also include an evaluation of these additional materials. Therefore, the remainder of the first year of this grant was devoted to initiating dose range studies with diesel emission particles using the Saffiotti method.

This grant was terminated after the first year and the dose range studies were incorporated into and completed under EPA Grant. No. R806929-01-0 which was entered into on September 1, 1979.

Alan M. Shefner is with IIT Research Institute, Life Sciences Research Division, 10 West 35th Street, Chicago, IL 60616.
***Donald E. Gardner** is the EPA Project Officer (see below).*
The complete report, entitled "Respiratory Carcinogenicity of Diesel Fuel Emissions," (Order No. PB 81-230 955; Cost: $6.50, subject to change) will be available only from:
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Telephone: 703-487-4650
The EPA Project Officer can be contacted at:
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

☆ U.S. GOVERNMENT PRINTING OFFICE: 1981 757-012/7356

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati OH 45268

Postage and
Fees Paid
Environmental
Protection
Agency
EPA 335

Official Business
Penalty for Private Use $300